Remarks

Reconsideration of this Application is respectfully requested. Upon entry of the foregoing amendment, claims 48-75 are pending in the application, with claims 48, 52, 54, 60 and 62-75 being the independent claims. Claims 60, 63, 65, 67, 69, 71, 73 and 75 are sought to be amended. Support for these claim amendments can be found throughout the specification and the claims. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

I. Telephone Call Between Applicants' Representative and Examiner

During a telephone call on September 16, 2005 with Examiner Audet, Aaron Schwartz (Applicants' representative) informed the Examiner that the Decision on Petition regarding the lack of unity holding had been mailed out on August 24, 2005. The Examiner indicated that the case had not yet been docketed to him and recommended that Applicant refile the Amendment and Reply that was first filed on April 15, 2005. The filing of this Supplemental Amendment and Reply corrects inadvertant claim drafting errors and reiterates Applicants' previously presented arguments that are responsive to rejections under 35 U.S.C. § 112.

II. Decision on Petition and Previously Examined Claims

In the Office Action mailed on December 16, 2004, claims 48-61 were examined on the merits. Moreover, Mr. Bruce Kisluik (Director, Technology Center 1600) in his Decision on Petition notes "that all of . . . claims 48-61 would fall within the previously elected Group III and have all been examined." *See* Decision on Petition, page 5, first full paragraph, last sentence. Hence, Applicants' understanding based on the previous Office Action and from the Decision on Petition is that claims 48-61 possess unity of invention and should be examined together.

Applicants respectfully assert that claims 62-75 possess unity of invention with claims 48-61. Like claims 48-61, claims 62-75 are directed to methods of stimulating or inhibiting C-fibre neuron activity using lectins and conjugates thereof. Moreover, claims 62-75 will not require searching beyond that which was already done for claims 48-61. Accordingly, Applicants respectfully request that the Examiner consider all of claims 48-75 together.

III. Enablement Rejections Under 35 U.S.C. § 112, First Paragraph

Claims 48-61 are rejected under 35 U.S.C. § 112, first paragraph. In particular, the examiner has alleged that the specification "does not reasonably provide enablement for treatment of a C-fibre neuron associated diseases/conditions with any ECL conjugate, other than ECL- LH_N/A." Office Action, page 2, lines 14-16. Applicants respectfully traverse the rejection.

A. Legal Requirement for Setting forth a Prima Facie Case of Non-Enablement

Reflecting the decisions of the federal courts, the M.P.E.P. provides guidance to examiners regarding enablement rejections. *See* M.P.E.P., 8th ed., § 2164 (Rev. 2, May 2004). In particular, the M.P.E.P. states that "[i]n order to make a rejection, the examiner has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." *Id.* at §2164.04 (*citing In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993)). Moreover, any allegation doubting "the truth or accuracy of any statement in a supporting disclosure . . . [must be supported by] acceptable evidence or reasoning which is inconsistent with the contested statement." *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367 (CCPA 1971). As with the written description requirement, an enablement analysis must be performed from the perspective of the skilled artisan: "The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation." *United States v. Telectronics, Inc.*, 857 F.2d 778, 785, 8 USPQ2d 1217, 1223 (Fed. cir. 1988).

Moreover, the Federal Circuit has stated that "[t]he specification need not disclose what is well known in the art." *In re Buchner*, 929 F.2d 660, 661, 18 USPQ2d 1331, 1332 (Fed. Cir. 1991) (*see also Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1384, 231 USPQ 81, 94 (Fed. Cir. 1986) ("a patent need not teach, and preferably omits, what is well known in the art."), *cert. denied*, 480 U.S. 947 (1987); *Lindemann Maschinenfabrik GMBH v. American Hoist & Derrick Co.*, 730 F.2d 1452, 1463, 221 USPQ 481, 489 (Fed. Cir. 1984); *In re Myers*, 410 F.2d 420, 424 (C.C.P.A.

1969) ("A specification is directed to those skilled in the art and need not teach or point out in detail that which is well-known in the art.").

B. The Specification Enables the Claims for the Skilled Artisan

Although Applicants argue in section ***III.C.*** below that the Examiner has not set forth a *prima facie* case of non-enablement, this section is provided to direct the Examiner's attention to exemplary portions of the specification that enable the claims for the skilled artisan. This section also refers the Examiner to additional objective evidence which demonstrates that the claims are enabled.

1. The Claimed Methods are Enabled as to Any Conjugate-Free Galactosyl- or Glucosyl-Binding Lectin

Applicants respectfully stress that it is the **lectin component** of the present invention that is the biologically active molecule. The efficacy of this molecule has been demonstrated in the present specification for representative galactosyl-binding lectins ECL and IB4. *See, e.g.,* Specification, Examples 8, 14, 16, 18 and 19. The efficacy of this molecule has also been demonstrated in the present specification for a representative glucosyl-binding lectin, WGA. *See, e.g.,* Specification, Example 7. It is the lectin component of the compositions used in the claimed methods which target specific sugar residues, which are characteristic markers present on the cell surface of C-fibres. *See* three abstracts provided herewith as Exhibit 1. Thus, the efficacy of the compositions used in the claimed methods (either lectin alone or conjugated) stems from the lectin component of the composition.

Prior to the present invention, it would have been routine for a skilled person to select or obtain a galactosyl- or glucosyl-binding lectin as recited in the pending claims.

This is abundantly clear from the present specification, which confirms that such lectins were commercially available. *See, e.g.,* Specification, page 7, lines 9-13. Prior to the present application, such lectins could also be routinely extracted and purified from nature. *See, e.g.,* Specification, page 9, lines 7-9.

Hence, Applicants' specification clearly teaches the skilled artisan that galactosyl- or glucosyl-binding lectins can be used alone (i.e., absent any other conjugate) according to the newly claimed methods. Moreover, Applicants' specification clearly indicates that such lectins were either commercially available or could otherwise routinely be isolated. Thus, Applicants' specification fully enables the use of lectins (free of any conjugate) as the composition of the claimed methods.

2. The Claimed Methods are Enabled as to Any Endopeptidase-Free Conjugate of a Galactosyl- or Glucosyl-Binding Lectin

Consistent with the above comments, efficacy of the *conjugate* aspect of the present invention also stems from the lectin component. Thus, selection of an accompanying peptide or protein for use in a conjugate of the present invention would be routine to a skilled person as the peptide or protein need not provide any technical effect. In the context of the present invention, the peptide or protein component may be simply considered an inert "carrier" molecule. *See, e.g.,* Specification, page 10, lines 5-8. This has been confirmed by data presented in the present specification showing that a conjugate comprising lectin and an inert carrier molecule (*e.g.,* an endopeptidase-negative LH_N molecule) has efficacy in accordance with the present invention. *See, e.g.,* Specification, Example 17.

As is self-evident from the above, the only requirement of the peptide or protein component is that it lacks endopeptidase activity. In this regard, it would have been routine (prior to the present invention) for a skilled person to confirm that any such peptide or protein lacks endopeptidase activity. As objective evidence of this assertion, Applicants respectfully refer the Examiner to documents AS21 and AT21 cited in the Second Supplemental Infromation Disclosure Statement, filed in the captioned application on December 9, 2004. These documents are declarations filed under 37 C.F.R. § 1.132 submitted in Applicants' copending application 09/529,130.

Moreover, the skilled artisan would be able to make conjugates of galactosyl- or glucosyl-binding lectins suitable for use in the present invention. Basic conjugation and coupling reactions are illustrated in Applicants' specification, for example, Examples 3, 4, 9, 10, and 11. These examples illustrate conjugation and coupling of lectins that are representative of the two classes of lectin relevant to the present invention to a separate peptide or protein component. Any conventional conjugation or coupling chemistry may be employed to prepare a conjugate for use according to the claims. Applicants refer the Examiner to the aforementioned documents AS21 and AT21 as additional objective evidence regarding this assertion. Applicants also refer the Examiner to U.S. Patent No. 5,433,946 ("the '946 patent"), previously submitted as document AA1 in an Information Disclosure Statement filed on September 26, 2001. The Abstract of the '946 patent provides further objective evidence that the basic concept of coupling lectins to proteins or peptides would be considered routine by the skilled artisan.

Hence, Applicants' specification clearly teaches the skilled artisan that endopeptidase-free conjugates of galactosyl- or glucosyl-binding lectins can be used

according to the newly claimed methods. Applicants' specification also clearly indicates that such conjugates can routinely be made. Moreover, Applicants' have provided additional objective evidence that such conjugates can routinely be made. Thus, Applicants' specification fully enables the use of endopeptidase-free galactosyl- or glucosyl-binding lectins as the composition of the claimed methods.

3. The Claimed Methods are Enabled as to Administration of Either Conjugate-Free or Conjugated Galactosyl or Glucosyl Binding Lectins

Applicants' specification describes formulations and modes for administering either conjugate-free or conjugated galactosyl- or glucosyl-binding lectins according to the claimed methods. *See, e.g.,* Specification, pages 13-14. Particularly preferred administrations are described, for example, Examples 5, 6, 7, 8, 16, 18 and 19 of the specification. Hence, the claimed methods are enabled as to administration of either conjugate-free or conjugated galactosyl- or glucosyl-binding lectins.

C. A Prima Facie Case for a Non-Enablement Rejection Has Not Been Set Forth

1. The Skilled Artisan is Adequately Guided by Applicants' Specification

The Examiner has alleged that

> Enablement must be provided by the specification unless it is well known in the art. . . . A search of the prior art, as to ECL conjugates for treating C-fiber related disorders, revealed a very limited number of teachings directed to the specific invention of the present application, therefore, the use of ECL conjugates for treating C-fiber related disorders cannot be construed as being well known in the art, and thus reliance for enablement must stem from the specification.

Office Action, page 3, last paragraph. However, this statement misconstrues the level of guidance needed for the skilled artisan. Indeed, *in every novel and unobvious invention*

there will be a very limited number of teachings directed to the specific invention. If such teachings existed, the invention would lack novelty or be obvious. It is important to note that the claimed subject matter of the captioned application is free of the prior art.

The relevant question is whether the skilled person could reasonably make and use lectins or conjugates thereof that possess the requisite properties, and thus reproduce the claimed method(s). Here, Applicants' specification clearly identifies galactosyl and glucosyl binding lectins as having a biological effect useful for the claimed methods. Guided by this new and unobvious teaching, the skilled artisan will readily understand that such lectins can be used in an unconjugated or conjugated form. Where they are used in a conjugated form, the skilled artisan can couple the lectin to a peptide or protein using any number of well known and routine coupling techniques. *See* documents AS21 and AT21 cited in the Second Supplemental Infromation Disclosure Statement, filed in the captioned application on December 9, 2004.

The Examiner has not provided *any* evidence why the skilled artisan could only practice Applicants' invention with undue experimentation. Such evidence should begin with a description of the skilled artisan and his or her knowledge to provide the proper perspective and framework from which to evaluate whether Applicants' claims are enabled. However, the Examiner entirely fails to define the skilled artisan or the knowledge generally known to him or her at the time the application was filed. Hence, the Examiner has not set forth a *prima facie* case that the claims are not enabled by the specification.

2. Scope of Lectin or Lectin Conjugate

The Examiner has also alleged that, because "[t]here are no working examples to indicate whether other ECL conjugates would be enabled (and what the structure/function of these are)," the skilled artisan would only be able to practice the claimed invention through undue experimentation. Office Action, page 4, first full paragraph. The Examiner's statement appears to be directed to both the scope of lectin and the scope of the peptide or protein used in a conjugate.

Regarding selection of the lectin component of the present invention, the pending claims are concerned with only two well-characterized classes of lectin.[1] Thus, there can be no undue burden in selecting and using such molecules. Moreover, Applicants have demonstrated in the present specification that these molecules modulate C-fibre activity. In this regard, the only relevant consideration in the context of the present invention is their ability to bind glucose or galactose residues on C-fibres. By definition, all galactosyl-binding lectins bind to galactosyl residues and all glucosyl-binding lectins bind to glucose residues. Hence, any galactosyl- or glucosyl-binding lectin would be suitable for use in the present invention. Moreover, the Examiner has not provided *any* evidence (or even reasoning) to support the allegation that selection of a lectin is unduly burdensome for the skilled artisan.

Regarding selection of the peptide or protein component of the present invention, as discussed above, this molecule is not relevant to efficacy considerations. Thus, consistent with lines 14-15 on page 10 of the specification, a skilled person would

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1 Lectins are routinely classified according to the sugar residues to which they bind. *See* documents AR15 and AT15 cited in Applicants' Second Supplemental IDS, filed December 9, 2004.

consider any peptide or protein to be suitable for use in the present invention, so long as the peptide or protein is free from endopeptidase activity, which is a readily testable property. Again, Applicants have demonstrated efficacy for one such inert peptide or protein molecule. Moreover, the Examiner has not provided any evidence (or even reasoning) to support his lack of enablement assertion. Hence, the skilled artisan would not face undue experimentation in order to select a peptide or protein with which to make a lectin conjugate.

3. Scope of LH_N Serotype

Applicants note that the Examiner appears to question the scope of LH_N. In particular, in stating that the specification "does not reasonably provide enablement for treatment of a C-fibre neuron associated diseases/conditions with any ECL conjugate, other than ECL- LH_N/A," the Examiner appears to be stating that a galactosyl- or glucosyl-binding lectin conjugated to LH_N is only enabled where the LH_N is derived from botulinum neurotoxin serotype A. To the extent the Examiner intended to make such an enablement scope rejection, Applicants traverse the rejection.

Such a rejection is unreasonable for at least three reasons. First, as mentioned above, the peptide or protein component of a conjugate of the present invention is immaterial to efficacy. Secondly, Clostridial neurotoxins have been well-known for many years, and collectively form a class of very closely, structurally related molecules. *See* Exhibit 2, provided herewith. Thus, having demonstrated efficacy of a conjugate comprising an inert serotype A component (see Example 17 of the present specification), a skilled person would expect efficacy with conjugates comprising corresponding inert peptide or protein components from other Clostridial serotypes. Thirdly, the Examiner

has provided no support for his assertion that, despite clear evidence in the present specification in favor conjugates comprising inert serotype A components, conjugates containing corresponding inert non-serotype A components would not have efficacy.

D. Summary of Enablement Rejection

The Examiner may properly withdraw the enablement rejection of claims 48-61 because Applicants' specification adequately enables the skilled artisan as to how to make and use galactosyl- or glucosyl-binding lectins or conjugates thereof according to the claimed methods. Moreover, the rejection may properly be withdrawn because a *prima facie* case in support of the rejection has not been set forth. Accordingly, Applicants request that the Examiner reconsider and withdraw the enablement rejection of claims 48-61.

IV. Indefiniteness Rejections Under 35 U.S.C. § 112, Second Paragraph

Claims 48-61 are rejected under 35 U.S.C. 112, second paragraph. In particular, the Examiner alleges that these claims are "indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention." Office Action, page 4. In particular, the Examiner alleges that

> Applicant was required to elect a single compound, and identifying it's chemical structure, as the invention (Supplemental Restriction). This requirement still has not been met (i.e. a specific lectin, for instance, the ECL conjugate ECL-LH_N/A) and the claims thus remain indefinite as to what constitutes the elected invention. As drafted, the claimed invention is essentially unsearchable (other than the elected group) because the instant claims do not contain a distinguishable structure (i.e. ECL-LH_N/A) that may be searched.

Office Action, pages 4-5. Applicants respectfully traverse the rejection.

A. Status of Claims Regarding Unity of Invention

As described in section ***II.*** above, the Office Action mailed on December 16, 2004, examined claims 48-61 on the merits. Moreover, Mr. Bruce Kisluik (Director, Technology Center 1600) in his Decision on Petition notes "that all of . . . claims 48-61 would fall within the previously elected Group III and have all been examined." *See* Decision on Petition, page 5, first full paragraph, last sentence. Hence, Applicants' understanding based on the previous Office Action and from the Decision on Petition is that claims 48-61 possess unity of invention and should be examined together.

Applicants also note that all pending claims are directed to stimulating or inhibiting C-fibre neuron activity using galactosyl- or glucosyl-binding lectins or such lectins coupled to a peptide or protein. Although these claims (or previous versions of the claims) have been searched and examined twice (*see* Office Actions mailed June 21, 2004 and December 16, 2004), these claims have not been rejected in light of any prior art. Because all of these claims are directed to modulating C-fibre neuron activity using an agent comprising a galactosyl- or glucosyl-binding lectin, Applicants respectfully assert that the claims possess unity of invention and should be examined together.

B. Previous Election

Notwithstanding that Applicants believe that the indefiniteness rejection under 35 U.S.C. §112, second paragraph is improper, Applicants have already provided the Examiner with a basis on which to perform the search: *Erythrina cristagalli* lectin. *See*

Reply to Restriction Requirement at page 2, filed February 27, 2004.[2] Moreover, Applicants previously provided the following information:

> Structural information for *Erythrina cristagalli* lectin is provided, for example, by Iglesias, J. L. *et al.*, *Eur. J. Biochem.*, *123*: 247-252 (1982) ("Iglesias *et al.*"), which is referred to in Applicants' Specification at page 18, lines 5-6. Iglesias *et al.* was previously cited as document AR4 in Applicants' Information Disclosure Statement filed on September 26, 2001, and an additional copy is provided herewith.

Id. at page 2, second paragraph.

Accordingly, it is believed that the Examiner has a basis on which to form a search of the claims.

C. Breadth Does Not Equate to Indefiniteness

Applicants wish to remind the Examiner that a claim's breadth does not make it indefinite. *See, e.g.,* M.P.E.P. 8th ed., § 2173.04 Breadth Is Not Indefiniteness (rev. 2, May 2004). This concept was recently upheld by the Court of Appeals for the Federal Circuit. *SmithKline Beecham Corp. v. Apotex Corp.* 74 USPQ2d 1396, 1404 (Fed. Cir. 2005).

Here, independent claims 48 and 52 are genus method claims directed to the use of galactosyl- or glucosyl-binding lectins. Independent claims 54 and 60 are genus method claims directed to the use of conjugates of galactosyl- or glucosyl-binding lectins. Galactosyl- or glucosyl-binding lectins have a distinguishable structure and a

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2 In the Reply to Restriction Requirement filed February 27, 2004, Applicants elected Group III, directed to a method of treating a disease or condition comprising administering an effective amount of a lectin. Because this election was directed to lectins (as opposed to a conjugate of a lectin), Applicants regret any confusion that may have arisen from the following statement (found in the first paragraph of page 2 of the Reply to Restriction Requirement): "Applicants also elect the

common function. Hence, the breadth of these claims encompass methods of inhibiting or stimulating C-fibre neuron activity using galactosyl- or glucosyl-binding lectins or conjugates thereof. As described in the section that follows, such lectins or conjugates thereof represents a class of compounds readily understood and discernible to the skilled artisan.

D. The Skilled Artisan Understands the Meaning of the Claims

As described by the M.P.E.P., the legal standard for determining whether claims are definite include consideration of i) the specification, ii) prior art teachings and iii) the claim interpretation that would be given by the skilled artisan at the time the invention was made. *See* M.P.E.P., 8th ed., § 2173.02 (rev. 2, May 2004).

Here, the claims are directed to methods employing galactosyl- or glucosyl-binding lectins or conjugates thereof. As described in section ***III.*** above, the specification adequately and clearly describes the meaning of such lectins or conjugates thereof. Moreover, section ***III.*** above describes prior art teachings indicating that it would have been routine for a skilled person to select or obtain such lectins. Section ***III.*** also describes how the skilled artisan would understand the meaning of such conjugates, which are claimed using the recitation "lectin coupled to a peptide or protein."

Applicants also note that the Examiner has provided no evidence or reasoning to explain why the skilled artisan upon reading Applicants' specification would find the claims to be indefinite.

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specific conjugate comprising *Erythrina cristagalli* lectin." Use of the term "conjugate" in this statement is mistaken and regretted.

Hence, the skilled artisan would have no difficulty in understanding the meaning of Applicants' claims directed to methods of inhibiting or stimulating C-fibre neuron activity using galactosyl- or glucosyl-binding lectins or conjugates thereof.

In summary, Applicants assert that claims 48-61 are not indefinite. Accordingly, Applicants respectfully request that the rejection under 35 U.S.C. § 112, 2nd paragraph be withdrawn.

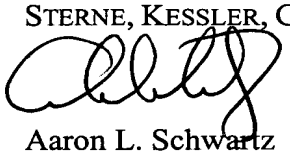
Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.



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